IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT :	Hirst *et al.*	Confirmation No.: 8699	
SERIAL NUMBER. :	09/674,935	**EXAMINER :**	Jana A. Hines
FILING DATE :	December 21, 2000	**ART UNIT :**	1645
FOR :	VACCINE		

MAIL STOP AMENDMENT
Commissioner for Patents
P. O. Box 1450
Arlington, VA 22313-1450

DECLARATION UNDER 37 CFR 1.132

I, Neil A. Williams, of Woodlyn Cottage, Birch Hill, Cheddar, Somerset, UK, declare and state that:

1. I am a co-inventor in the above-identified patent application ("the Application"). I have reviewed the Office Action mailed October 15, 2009. I understand that claims 38, 41, 42, 44, 54, 55, 58, 59, and 61 are rejected under 35 U.S.C. §103(a) as being obvious over Richards *et al.*, (Vaccine, 15(10): 1065-1069 (1997)) in view of Williams et al., International Patent Application WO 97/02045 (hereinafter, "Williams"), for which I am also an inventor.

2. I understand that the present claims are directed to methods of generating a T-lymphocyte cell-mediated protective immune response against a herpes virus infection comprising co-administering to the mammal a therapeutically effective amount of Escherichia coli heat labile enterotoxin B subunit (EtxB), and an antigen, wherein the EtxB is free from whole toxin and is not linked to the antigen, wherein the antigen is a virus antigen from the herpes virus family.

3. Williams actually teaches away from the use of EtxB to generate a T-lymphocyte cell-mediated protective immune response. Williams teaches that EtxB protein induces

differential effects on lymphocyte populations, including a specific depletion of CD8+ T cells. Specifically, Williams states as follows:[1]

> The basis for all aspects of the present invention is the finding that EtxB (the pure B-subunit of the E. coli heat labile enterotoxin) binds to GM1-ganglioside receptors which are found on the surfaces of mammalian cells, and that this binding induces differential effects on lymphocyte populations, including a specific depletion of CD8+ T cells and an associated activation of B cells. These effects are absent when a mutant EtxB protein lacking GM1 binding activity is employed.
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> Agents in accordance with the present invention have been found to modulate lymphocyte populations leading to the induction of apoptosis in CD8+ T cells, the enhanced activation of CD4+ cells and polyclonal activation of B cells. These events are likely to shift the immune response towards induction of Th2 associated cytokines. Such responses to self or crossreacting antigens are understood to mediate protection for certain autoimmune diseases.

In this regard, Williams relates to the activation of a humoral immune response, rather than the recited T lymphocyte cell-mediated protective immune response.

4. In contrast, data presented in the present invention shows that EtxB can lead to the activation of T-cells which secrete γIFN. Accordingly, the data presented in the Application would have been unexpected to a person of ordinary skill in the art. Specifically, Example 11 of the specification summarizes the results of experiments where mice were infected with a strain of HSV-1 by scarification into the cornea in combination with rEtxB. The results showed that T-cells were capable of responding to HSV-1 and that lymph node cells taken from mice produced predominantly the Th1 associated cytokine y-interferon (γ-IFN). Thus, the present specification shows that EtxB may be used to produce a Th1 associated immune response — *i.e.*, a T lymphocyte cell-mediated protective immune response, which includes, for example, proliferation of cytotoxic $CD8^+$ T cells.

[1] Williams at page 1, line 34 to page 2, line 6 and page 2, lines 20-28.

5. I hereby declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by a fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Neil A. Williams
Signed this _29th_ day of March, 2010

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